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UNITED STATES PATENT APPLICATION OF

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FOR

1-ARYL-2-HYDROXYETHYL AMIDES
AS POTASSIUM CHANNEL OPENERS

1-ARYL-2-HYDROXYETHYL AMIDES
AS POTASSIUM CHANNEL OPENERS

CROSS-REFERENCE TO RELATED APPLICATIONS

5   This is a non-provisional application which claims the benefit of U.S.
Provisional Application Number 60/428,338 filed November 22, 2002.

FIELD OF THE INVENTION

10   The present invention is directed to novel aryl hydroxyethyl amide
derivatives which are modulators of KCNQ potassium channels and are therefore
useful in treating disorders responsive to the modulation of the potassium
channels. The present invention also provides a method of treatment with the
novel aryl hydroxyethyl amide derivatives and to pharmaceutical compositions
15   thereof.

BACKGROUND OF THE INVENTION

         Potassium (K^+) channels are considered to be the most diverse class of ion
channels and have several critical roles in cell function. This has been
20   demonstrated in neurons where K^+ channels are responsible, in part, for
determining cell excitability by contributing to membrane repolarization
following depolarization, resting membrane potential, and regulation of
neurotransmitter release. The M-current has long been described, by
electrophysiology recording methods and by pharmacology, as a dominant
25   conductance in controlling neuronal excitability. Pharmacological activation or
suppression of M-currents by small molecules could have profound effects in
controlling neuronal excitability. Recently, Wang et al., Science, 282:1890-1893,
(1998) reported that co-assembly of the KCNQ2 and KCNQ3 potassium channels
underlies the native M-current in neurons.
30   Activation or opening of the KCNQ channel(s), particularly the KCNQ2
or KCNQ2/3 channel(s), mutated or wild type, may prove to be beneficial in
increasing hyperpolarization of neurons, thereby resulting in protection from
abnormal synchronous firing during a migraine attack. The present invention

provides a solution to the problem of abnormal synchronous firing of neurons related to migraine headache by demonstrating that modulators, preferably openers, of KCNQ potassium channels increases hyperpolarization of neurons which protects against abnormal synchronous neuron firing involved in migraine

5   attacks.

Although the symptom pattern varies among migraine sufferers, the severity of migraine pain justifies a need for vigorous, yet safe and effective, treatments and therapies for the great majority of cases. Needed in the art are agents that can be used to combat and relieve migraine (and diseases similar to

10   and mechanistically related to migraine), and even prevent the recurrence of migraine. Also needed are anti-migraine agents which are effective in the treatment of acute migraine, as well as in the prodrome phase of a migraine attack. Thus, a clear goal in the art is to discover new, safe, nontoxic and effective anti-migraine compounds for use as drugs, and in anti-migraine

15   compositions and treatments.

Because migraine afflicts a large percentage of the population, there is a need to discover compounds and agents that are useful in therapeutics and treatments, and as components of pharmaceutical compositions, for reducing, ameliorating, or alleviating the pain and discomfort of migraine headache and

20   other symptoms of migraine. The present invention satisfies such a need by providing compounds that function as openers of the KCNQ family of potassium channel proteins to serve as anti-migraine agents or drugs and to comprise compositions to treat migraine, as described herein.

A broad range of cinnamide compounds are known and new compounds

25   continue to be reported with a broad range of utility. Some of these compounds can be found in the disclosures of WO 00/07993 published February 17, 2000, EP 810220A1, published December 3, 1997, U.S.4,927,838 issued May 22, 1990 to Guthrie, et al., U.S.6,046,239 issued April 4, 2000 to Lennox, et al., WO 00.42013, published July 20, 2000, WO 01/10381 published February 15, 2001,

30   WO 01/10380 published February 15, 2001, JP45-14291 published May 21, 1970, and JP2-138159 published May 28, 1990. The compounds described in these patents are distinct from those of the present invention.

SUMMARY OF THE INVENTION

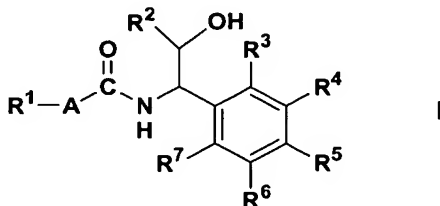The present invention provides novel aryl hydroxyethyl amides and related derivatives having the general Formula I

I
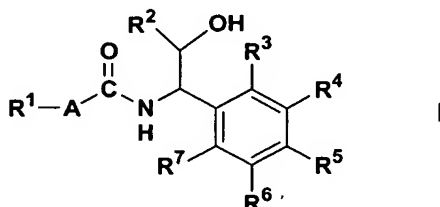
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and A are as defined below, or a nontoxic pharmaceutically acceptable salt, solvate or hydrate thereof which are openers or activators of KCNQ potassium channels. The present invention also provides pharmaceutical compositions comprising said aryl hydroxyethyl amides and to the method of treatment of disorders sensitive to KCNQ potassium channel opening activity such as migraine or a migraine attack, bipolar disorders, epilepsy, acute and chronic pain and anxiety.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel aryl hydroxyethyl amides and related derivatives which are modulators of the KCNQ potassium channels and which have the general Formula I or a pharmaceutically acceptable salt thereof

I

wherein R^1 is selected from the group consisting of pyridinyl, 3-quinolinyl, 2-thienyl, furanyl, C_{3-6} cycloalkyl and phenyl optionally substituted with substituent independently selected from the group consisting of halogen, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, trifluoromethoxy and nitro; A is $-CH=CH-$ or $-(CH_2)_n-$; R^2 is hydrogen or hydroxymethyl; n is an integer of 0, 1 or 2; R^4 is selected from

the group consisting of di(C_{1-4} alkyl)amino, trifluoromethoxy and optionally substituted morpholin-4-yl, morpholin-4-ylmethyl, pyridinyl, pyrimidinyl, piperazinyl, and pyrazinyl with one or two substituents in which said substituent is independently selected from the group consisting of C_{1-4} alkyl, aminomethyl,

5   hydroxymethyl, chloro or fluoro; R^5 is hydrogen or fluoro; or R^4 and R^5 taken together is –CH=CH-CH=CH- optionally substituted with a substituent independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl and trifluoromethoxy; and R^3, R^6, and R^7 are each independently hydrogen or fluoro.

10   The present invention also provides a method for the treatment or alleviation of disorders associated with KCNQ potassium channel polypeptides and, in particular, human KCNQ potassium channel polypeptides in a mammal in need thereof which comprises administering together with a conventional adjuvant, carrier or diluent a therapeutically effective amount of a compound of

15   Formula I or a pharmaceutically acceptable salt thereof. Preferably, the compounds of Formula I are useful in the treatment of migraine or a migraine attack, cluster headaches, bipolar disorder, convulsions, mania, acute mania, epilepsy, anxiety, depression, schizophrenia, functional bowel disorders, stroke, traumatic brain injury, multiple sclerosis, neurodegenerative disorders or

20   alleviating pain such as musculoskeletal pain, post operative pain, surgical pain, inflammatory pain, neuropathic pain such as diabetic neuropathy and pain associated with cancer and fibromyalgia.

The term "pain" as used herein and in the claims means all types of acute and chronic pain, such as neuropathic pain, post-operative pain, chronic lower

25   back pain, cluster headaches, herpes neuralgia, phantom limb pain, central pain, dental pain, opioid-resistant pain, visceral pain, surgical pain, bone injury pain, pain during labor and delivery, pain resulting from burns, including sunburn, post partum pain, migraine, angina pain, and genitourinary tract-related pain including cystitis and the term also is intended to include nociceptive pain or nociception.

30   The term "C_{1-4} alkyl" as used herein and in the claims means straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and *tert*-butyl. The term "C_{1-4} alkoxy" as used herein and in the claims

means an oxygen substituted with straight or branched chain alkyl groups and includes groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, and *tert*-butoxy. The term "halogen" as used herein and in the claims is intended to include bromine, chlorine, iodine and fluorine.

5   As the compounds of the present invention contain a substituted carbon-carbon double bond as part of the structure, the compounds of the invention exist in either of two geometric isomeric forms, namely as cis or trans isomers. Preferred are the trans isomers in which the group R^i and the amide group, C(O)NH, are trans to each other when A is –CH=CH-. As the compounds of the

10   present invention possess an asymmetric carbon atom, such as the carbon adjacent to the amide nitrogen and to which the phenyl is attached, the present invention includes the racemate as well as the individual enantiomeric forms of the compounds of Formula I as described herein and in the claims. Preferred embodiments of compounds of Formula I include the racemate, a single

15   enantiomer, and in certain instances a single enantiomer wherein the carbon adjacent to the amide nitrogen and to which the phenyl is attached has the *(S)* stereochemistry. Mixtures of isomers of the compounds of Formula I or chiral precursors thereof can be separated into individual isomers according to methods which are known per se, e.g. fractional crystallization, adsorption

20   chromatography or other suitable separation processes. Resulting racemates can be separated into antipodes in the usual manner after introduction of suitable salt-forming groupings, e.g. by forming a mixture of diastereosiomeric salts with optically active salt-forming agents, separating the mixture into diastereomeric salts and converting the separated salts into the free compounds. The

25   enantiomeric forms may also be separated by fractionation through chiral high pressure liquid chromatography columns, according to procedures described herein.
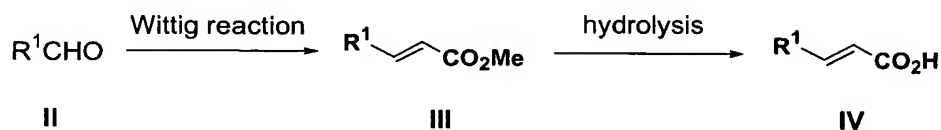
       Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms including hydrated forms such as monohydrate,

30   dihydrate, trihydrate, hemihydrate, tetrahydrate and the like. The products may be true solvates, while in other cases, the products may merely retain adventitious solvent or be a mixture of solvate plus some adventitious solvent. It should be

appreciated by those skilled in the art that solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

5   In the method of the present invention, the term "therapeutically effective amount" means the total amount of each active component of the method that is sufficient to show a meaningful patient benefit, i.e., amelioration or healing of conditions which respond to modulation of the KCNQ potassium channels. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to

10 combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. The term "KCNQ" as used herein and in the claims means the family of KCNQ2, KCNQ3, KCNQ4, and KCNQ5 potassium channel polypeptides as well as heteromultimers of different individual family members which include but are not limited to

15 KCNQ2/3, KCNQ2/5 and KCNQ3/5. The terms "treat, treating, treatment" as used herein and in the claims means preventing, alleviating or ameliorating diseases and/or symptoms associated with dysfunction of cellular membrane polarization and conductance of human KCNQ2, KCNQ3, KCNQ4, and KCNQ5 potassium channel polypeptides and, in particular, migraine and/or symptoms that

20 precede a full-blown migraine attack, neuropathic pain, mania and anxiety.

        The general procedures used to synthesize intermediates and the compounds of Formula I are described in Reaction Schemes 1-4 and are illustrated in the preparations and examples. Reasonable variations of the described procedures, which would be evident to one skilled in the art, are

25 intended to be within the scope of the present invention.

Reaction Scheme 1

$$R^1CHO \xrightarrow{\text{Wittig reaction}} R^1 \diagup\diagdown\diagup CO_2Me \xrightarrow{\text{hydrolysis}} R^1 \diagup\diagdown\diagup CO_2H$$

        II   III   IV

30

Reaction Scheme 1 depicts the preparation of cinnamic acid derivatives useful as intermediates in the synthesis of compounds of Formula I. Step 1 of Reaction Scheme 1 depicts the Wittig reaction of an appropriate aldehyde or ketone of Formula II with an appropriate Wittig reagent to provide the methyl

5   ester of Formula III. Hydrolysis of the methyl ester of Formula III can be accomplished using an appropriate base such as sodium hydroxide or lithium hydroxide in an appropriate solvent followed by acidification with an appropriate acid such as 1N hydrochloric acid to provide the cinnamic acid of Formula IV.

10   Reaction Scheme 2
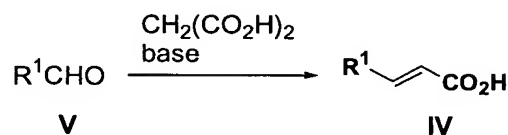
Reaction Scheme 2 depicts an alternative preparation of a cinnamic acid

15   derivative of Formula IV which can be then used to prepare compounds within general Formula I.

Reaction Scheme 3

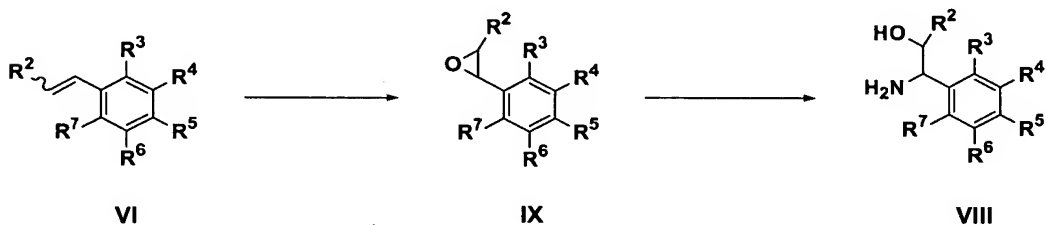20   VI   VII   VIII
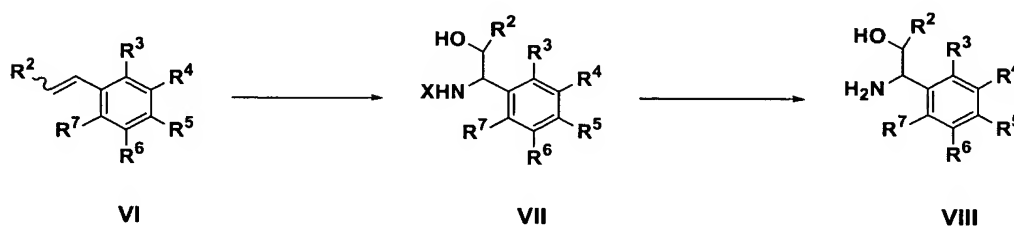
Reaction Scheme 3 depicts a general method useful for the preparation of amines of Formula VIII which are useful intermediates for the preparation of compounds of Formula I. Compound of Formula VI was converted to compound

25   of Formula VII, wherein X is $CO(O)^tBu$ or $C(O)OCH_2C_6H_5$, via catalytic asymmetric aminohydroxylation following the procedures of Sharpless and co-

workers (J. Amer. Che. Soc., 1998, Vol. 120, No. 6, pp1207-1217). Deprotection
of compound of Formula VII can be accomplished by hydrolysis under acidic
conditions such as 1N hydrochloric acid or catalytic hydrogenation to afford
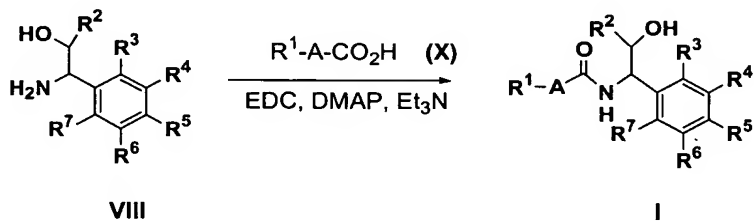compound of Formula VIII.

5

Reaction Scheme 4

VI   IX   VIII

10   Reaction Scheme 4 depicts an alternative method useful for the
preparation of amines of Formula X. Compound of Formula VI underwent
epoxidation under epoxidation conditions such as mCPBA (meta-
chloroperoxybenzoic acid) or methyltrioxorhenium and hydrogen peroxide to
give compound of Formula IX. The compound of Formula IX can be converted
15   to compound of Formula VIII by treatment with azidotrimethylsilane followed by
aluminum isopropyoxide.

Reaction Scheme 5

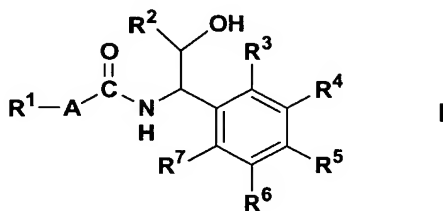20   VIII   I

Reaction Scheme 5 depicts the preparation of compounds of general
Formula I from the acid of general Formula X and amine of general Formula
VIII. The coupling of the acid, X, and amine, VIII is carried out by methodology
25   well known in the art for the conversion of an acid and an amine to form an

amide. Useful reactive derivatives of the acid of Formula X include, but are not limited to, activated esters, reactive mixed anhydrides, and acid halides (such as the acid chloride, prepared e.g. with thionyl chloride or oxalyl chloride). A preferred method is to condense the acid of Formula X with the amine of Formula

.5   VIII in the presence of an appropriate condensing agent, for example, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) or dicyclohexylcarbodiimide (DCC), and a basic tertiary amine, such as 4-dimethylaminopyridine (DMAP), in an inert solvent such as dichloromethane. The more preferred method is to couple the acid of Formula X with the amine of Formula VIII in the presence of

10   1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride (EDC) in the presence of 4-dimethylaminopyridine (DMAP), triethylamine (Et_3N), in dichloromethane.

In one embodiment, the present invention includes compounds of Formula I or a pharmaceutically acceptable salt thereof

15

wherein R^1 is selected from the group consisting of pyridinyl, 3-quinolinyl, 2-thienyl, furanyl, C_{3-6} cycloalkyl and phenyl optionally substituted with substituent

20   independently selected from the group consisting of halogen, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, trifluoromethoxy and nitro; A is –CH=CH- or –$(CH_2)_n$-; R^2 is hydrogen or hydroxymethyl; n is an integer of 0, 1 or 2; R^4 is selected from the group consisting of di(C_{1-4} alkyl)amino, trifluoromethoxy and optionally substituted morpholin-4-yl, morpholin-4-ylmethyl, pyridinyl, pyrimidinyl,

25   piperazinyl, and pyrazinyl with one or two substituents in which said substituent is independently selected from the group consisting of C_{1-4} alkyl, aminomethyl, hydroxymethyl, chloro or fluoro; R^5 is hydrogen or fluoro; or R^4 and R^5 taken together is –CH=CH-CH=CH- optionally substituted with a substituent

independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy,
trifluoromethyl and trifluoromethoxy; and R^3, R^6, and R^7 are each independently
hydrogen or fluoro.

In a preferred embodiment, the present invention includes compounds of
Formula Ia or a pharmaceutically acceptable salt thereof
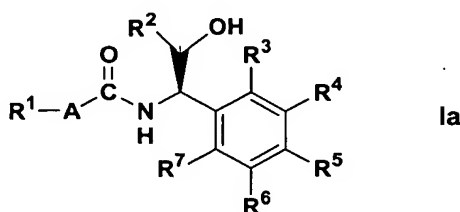
Ia

wherein R^1 is selected from the group consisting of pyridinyl, 3-quinolinyl, 2-
thienyl, furanyl, C_{3-6} cycloalkyl and phenyl optionally substituted with substituent
independently selected from the group consisting of halogen, C_{1-4} alkyl, C_{1-4}
alkoxy, trifluoromethyl, trifluoromethoxy and nitro; A is $-CH=CH-$ or $-(CH_2)_n-$;
R^2 is hydrogen; n is an integer of 0, 1 or 2; R^4 is selected from the group
consisting of di(C_{1-4} alkyl)amino, trifluoromethoxy and optionally substituted
morpholin-4-yl, morpholin-4-ylmethyl, pyridinyl, pyrimidinyl, piperazinyl, and
pyrazinyl with one or two substituents in which said substituent is independently
selected from the group consisting of C_{1-4} alkyl, aminomethyl, hydroxymethyl,
chloro or fluoro; R^5 is hydrogen or fluoro; or R^4 and R^5 taken together is −
CH=CH-CH=CH- optionally substituted with a substituent independently
selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl and
trifluoromethoxy; and R^3, R^6, and R^7 are each independently hydrogen or fluoro.

Preferred compounds for use in the method of the present invention
include the compounds of Formula I listed below:

(*R*)- N-[2-hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-3-phenyl-propionamide;

(*R*)- 3-(2-fluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-
acrylamide;

(*R*)- 3-(3-fluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-
acrylamide;

(*R*)- 3-(2,4-difluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide;

(*R*)- N-[1-(4-fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-3-(2-fluoro-phenyl)-acrylamide;

5   (*R*)- N-[1-(4-fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-3-(3-fluoro-phenyl)-acrylamide;

(*R*)- N-[1-(4-fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-3-(4-fluoro-phenyl)-acrylamide;

(*R*)- 3-(2,4-difluoro-phenyl)-N-[1-(4-fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-

10   ethyl]-acrylamide;

(*R*)- 3-(3-fluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide;

(*R*)- 3-(4-fluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide;

(*R*)- 3-(2,4-difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide;

(*R*)- 3-(3,4-difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide;

15   (R)-4-fluoro-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-benzamide;

(R)-2,3-difluoro-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-benzamide;

(R)-2,4-difluoro-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-benzamide;

(R)-3,4-difluoro-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-benzamide;

(R)-2-(2,4-difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acetamide;

20   (R)-3-(2-fluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-propionamide;

(R)-3-(3-fluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-propionamide;

(R)-3-(4-fluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-propionamide;

(R)-3-(2,4-difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-propionamide;

25   (*R*)- 3-(2-fluoro-phenyl)-N-[2-hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-acrylamide;

(*R*)- 3-(3-fluoro-phenyl)-N-[2-hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-acrylamide;

(*R*)- 3-(4-fluoro-phenyl)-N-[2-hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-

30   acrylamide;

(*R*)- 3-(2,4-difluoro-phenyl)-N-[2-hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-acrylamide;

(1R,2S)- N-(2,3-dihydroxy-1-naphthalen-2-yl-propyl)-3-(2-fluoro-phenyl)-acrylamide;

(1R,2S)- 3-(2,4-difluoro-phenyl)-N-(2,3-dihydroxy-1-naphthalen-2-yl-propyl)-acrylamide;

5   (1R,2S)- 3-(3,4-difluoro-phenyl)-N-(2,3-dihydroxy-1-naphthalen-2-yl-propyl)-acrylamide; and

(1R,2S)- 3-(3,5-difluoro-phenyl)-N-(2,3-dihydroxy-1-naphthalen-2-yl-propyl)-acrylamide;

or a pharmaceutically acceptable salt thereof.

10

BIOLOGICAL ACTIVITY

KCNQ Methods and Results

Potassium (K^+) channels are structurally and functionally diverse families
15   of K^+-selective channel proteins which are ubiquitous in cells, indicating their
central importance in regulating a number of key cell functions [Rudy, B.,
Neuroscience, 25: 729-749 (1988)]. While widely distributed as a class, K^+
channels are differentially distributed as individual members of this class or as
families. [Gehlert, D.R., et al., Neuroscience, 52: 191-205 (1993)]. In general,
20   activation of K^+ channels in cells, and particularly in excitable cells such as
neurons and muscle cells, leads to hyperpolarization of the cell membrane, or in
the case of depolarized cells, to repolarization. In addition to acting as an
endogenous membrane voltage clamp, K^+ channels can respond to important
cellular events such as changes in the intracellular concentration of ATP or the
25   intracellular concentration of calcium (Ca^{2+}). The central role of K^+ channels in
regulating numerous cell functions makes them particularly important targets for
therapeutic development. [Cook, N.S., Potassium channels: Structure,
classification, function and therapeutic potential. Ellis Horwood, Chinchester
(1990)]. One class of K+ channels, the KCNQ family exemplified by KCNQ2,
30   KCNQ2/3 heteromultimers, and KCNQ5, is regulated by transmembrane voltage
and plays a potentially important role in the regulation of neuronal excitability

[Biervert, C., et al., Science, 279: 403-406 (1998); Lerche, C. et al., J. Biol. Chem. 275:22395-22400 (2000); Wang, H. et al., Science, 282:1890-1893 (1998)].

An opener of KCNQ channels, such as the KCNQ2 and KCNQ2/3 channel opener retigabine, exerts its cellular effects by increasing the open probability of these channels [Main J., Mol Pharmacol 58(2):253-62 (2000); Wickenden, A. et al., Mol. Pharm. 58:591-600 (2000)]. This increase in the opening of individual KCNQ channels collectively results in the hyperpolarization of cell membranes, particularly in depolarized cells, produced by significant increases in whole-cell KCNQ-mediated conductance.

Whole-cell patch-clamp recordings were made from an HEK 293 stable cell line expressing mKCNQ2 channels, maintained in culture for 1-2 days. Patch pipettes had initial resistances of 2.5-4 MΩ. Currents were recorded with an EPC-9 amplifier (HEKA, Lambrecht, Germany) controlled with software (Pulse, HEKA) run on a standard lab PC. Series resistance compensation was used during current recording, and set at 80%. The series resistance (R) and cell capacitance (C) were determined electronically by subtracting the capacitive currents at the onset and offset of a 5mV voltage step. The cancellation of whole-cell capacitive transients was virtually complete in all cells. Analog current signals were low-pass filtered at 2.9kHz using a four-pole Bessel filter -3dB) and stored on a local network server computer at a sampling rate of 1.5kHz. All recordings were performed at room temperature (20-22°C). The pipette solution contained (mM) : KCl, 150; CaCl$_2$, 2.5; EGTA, 5; MgCl$_2$, 1; HEPES, 10; pH to 7.3 with KOH, and Osmolality of 290-300 mOsm. The extracellular solution contained (mM) : NaCl, 140; KCl, 2.5; CaCl$_2$, 2.5; MgCl$_2$, 1; glucose, 10; HEPES, 10; pH to 7.3 with NaOH, and Osmolality of 305-310 mOsm

For analysis of agents effects on mKCNQ2 currents, the raw current records were displayed on the digital oscilloscope of the Pulse software application. Concentration response data were generated by measuring the difference in the steady-state amplitude of current in the presence of compound at the end of a 600 ms voltage-clamp step from a holding potential of –80mV. The concentration-response data were fitted with Hill-type equations:

$$I = I_{max}/(1+EC_{50}/[A]^{nH}),$$

where I is the steady-state current at a given concentration of agonist [A]; and I_{max}, EC_{50} and nH are parameters estimated from the curve fit. In some cases the
5 concentration-response data were fitted with equations consisting of the sum of two Hill-type components. Current-voltage (I/V) relationships for agonist-evoked currents were obtained by performing 600 ms voltage steps (-110 mV to +40 mV) in the absence and presence of agonist. The effect of the representative compounds of Formula I on KCNQ currents is listed in Table 1.

10

TABLE 1

Example No.	EC_{50} (μM) @ -40 mv)	I_{max} (%)
18	1.46	820
48	0.619	981

Thallium Assay Methods and Results

    A thallium flux assay was used to detect and characterize openers of
15 KCNQ potassium channels. The thallium assay is generally described in International application WO 02/31508 published April 18, 2002. More specifically, the thallium influx assay to detect compounds that block or open the voltage-gated K^+ channel KCNQ2 is described in Example IV of the published WO 02/31508 application.
20   For data analysis, the amplitude of the average of the negative controls was subtracted from all wells. The amplitudes of the test compounds were then compared to the value of four standard deviations of the negative control wells. The lowest concentration of a test compound sufficient to generate a signal amplitude greater than or equal to four standard deviations from the amplitude of
25 the negative controls was defined as the minimal active concentration.

    For generating EC_{50} values, compounds were serially diluted in 1:3 volume increments to produce a 10 point concentration series. EC_{50} values were calculated by fitting the resulting amplitudes to a single-site logistic equation.

EC_{50} was defined as the concentration of test compound required to yield 50% of the maximal response. Maximal response (Maximal opening) was the largest signal amplitude above the negative control generated by any concentration of a test compound.

5   The following Table 2 contains data which show that compounds of the present invention are openers of the KCNQ channels.

TABLE 2

Example No.	EC_{50} (μM)
47	0.039
48	0.503
49	0.354
55	0.144
58	0.892
106	1.44
111	0.98

10   In another embodiment, this invention includes pharmaceutical compositions comprising at least one compound of Formula I in combination with a pharmaceutical adjuvant, carrier or diluent.

In still another embodiment, this invention relates to a method of treatment or prevention of disorders responsive to opening of KCNQ potassium

15   channels in a mammal in need thereof, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I. Preferably, the compounds of Formula I are useful in the treatment of treatment of migraine or a migraine attack, cluster headaches, bipolar disorder, convulsions, mania, acute mania, epilepsy, anxiety, depression, schizophrenia, functional

20   bowel disorders, stroke, traumatic brain injury, multiple sclerosis, neurodegenerative disorders or alleviating pain such as musculoskeletal pain, post

operative pain, surgical pain, inflammatory pain, neuropathic pain such as diabetic neuropathy and pain associated with cancer and fibromyalgia.

For therapeutic use, the pharmacologically active compounds of Formula I will normally be administered as a pharmaceutical composition comprising as

5   the (or an) essential active ingredient at least one such compound in association with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable adjutants and excipients employing standard and conventional techniques.

The pharmaceutical compositions include suitable dosage forms for oral,

10   parenteral (including subcutaneous, intramuscular, intradermal and intravenous) bronchial or nasal administration. Thus, if a solid carrier is used, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form, or in the form of a troche or lozenge. The solid carrier may contain conventional excipients such as binding agents, fillers, tableting lubricants, disintegrants,

15   wetting agents and the like. The tablet may, if desired, be film coated by conventional techniques. If a liquid carrier is employed, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule, sterile vehicle for injection, an aqueous or non-aqueous liquid suspension, or may be a dry product for reconstitution with water or other suitable vehicle before use. Liquid preparations

20   may contain conventional additives such as suspending agents, emulsifying agents, wetting agents, non-aqueous vehicle (including edible oils), preservatives, as well as flavoring and/or coloring agents. For parenteral administration, a vehicle normally will comprise sterile water, at least in large part, although saline solutions, glucose solutions and like may be utilized. Injectable suspensions also

25   may be used, in which case conventional suspending agents may be employed. Conventional preservatives, buffering agents and the like also may be added to the parenteral dosage forms. Particularly useful is the administration of a compound of Formula I directly in parenteral formulations. The pharmaceutical compositions are prepared by conventional techniques appropriate to the desired

30   preparation containing appropriate amounts of the active ingredient, that is, the compound of Formula I according to the invention. See, for example,

Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, 17th edition, 1985.

The dosage of the compounds of Formula I to achieve a therapeutic effect will depend not only on such factors as the age, weight and sex of the patient and mode of administration, but also on the degree of potassium channel activating activity desired and the potency of the particular compound being utilized for the particular disorder of disease concerned. It is also contemplated that the treatment and dosage of the particular compound may be administered in unit dosage form and that the unit dosage form would be adjusted accordingly by one skilled in the art to reflect the relative level of activity. The decision as to the particular dosage to be employed (and the number of times to be administered per day is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect.

A suitable dose of a compound of Formula I or pharmaceutical composition thereof for a mammal, including man, suffering from, or likely to suffer from any condition as described herein is an amount of active ingredient from about 0.01 μg/kg to 10 mg/kg body weight. For parenteral administration, the dose may be in the range of 0.1 μg/kg to 1 mg/kg body weight for intravenous administration. For oral administration, the dose may be in the range about 0.1 μg/kg to 5 mg/kg body weight. The active ingredient will preferably be administered in equal doses from one to four times a day. However, usually a small dosage is administered, and the dosage is gradually increased until the optimal dosage for the host under treatment is determined.

However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances including the condition to be treated, the choice of compound of be administered, the chosen route of administration, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.

The following examples are given by way of illustration and are not to be construed as limiting the invention in any way inasmuch as many variations of the invention are possible within the spirit of the invention.

DESCRIPTION OF SPECIFIC EMBODIMENTS

Unless otherwise stated, solvents and reagents were used directly as obtained from commercial sources, and reactions were performed under a nitrogen atmosphere. Flash chromatography was conducted on Silica gel 60
5   (0.040-0.063 particle size; EM Science supply). ^{1}H NMR spectra were recorded on a Bruker DRX-500f at 500 MHz; a Bruker DPX-300B at 300 MHz; or a Varian Gemini 300 at 300 MHz . The chemical shifts were reported in ppm on the δ scale relative to δTMS = 0. The following internal references were used for the residual protons in the following solvents: $CDCl_3$ (δ_H 7.26), CD_3OD (δ_H 3.30)
10   and DMSO-d_6 (δ_H 2.50). Standard acronyms were employed to describe the multiplicity patterns: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad), app (apparent). The coupling constant (J) is in hertz. LC/MS was performed on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-VIS detector with Mass Spectrometry data determined using a Micromass
15   LC Platform in positive electrospray ionization mode (ESI+). Mass Spectrometry (MS) data was obtained using a standard flow injection technique on a Micromass LC Platform in positive electrospray ionization mode (ESI+) unless otherwise noted. High resolution mass spectrometry (HRMS) data was obtained using a standard flow injection technique on a Finnigan MAT 900 mass
20   spectrometer in electrospray ionization (ESI) mode. The analytical reverse phase HPLC method is as follows unless otherwise noted: Column YMC ODS-A C18 S7 (3.0 x 50 mm), Start %B = 0, Final %B = 100, Gradient Time = 2 min, Flow rate 5 ml/minutes. Wavelength = 220 nm, Solvent A = 10% MeOH - 90% H_2O – 0.1% TFA, Solvent B = 90% MeOH - 10% H_2O – 0.1% TFA; and R_t in min.
25   Preparative reverse phase HPLC was performed on a Shimadzu LC-8A automated preparative HPLC system with detector (SPD-10AV UV-VIS) wavelength and solvent systems (A and B) the same as above except where otherwise noted.

The following LCMS conditions were employed for the analysis of the
30   compounds of Examples 1–117 and are as follows:

a)   YMC Xterra C18 S5 4.6x50 mm; 0-100% gradient over 3 min; 4
       mL/min flow rate

b)   YMC ODS-A C18 S7 3.0x50 mm; 0-100% gradient over 2 min; 5
       mL/min flow rate

5   c)   YMC ODS S7 3.0x50 mm; 0-100% gradient over 2 min; 5 mL/min
       flow rate

d)   YMC Xterra C18 S7 3.0x50 mm; 0-100% gradient over 2 min; 4
       mL/min flow rate

e)   2Primeshere C18-HC 4.6x30 mm; (5 mM NH$_4$OAc) 0-100%
10   gradient over 2 min; 4 mL/min flow rate

f)   YMC ODS-A C18 S5 4.6 x 33 mm; 0-100% gradient over 2 min; 5
       mL/min flow rate

PREPARATION OF INTERMEDIATES

15

Preparation 1

Preparation of (R)- 2-Amino-2-(3-morpholin-4-ylmethyl-phenyl)-ethanol hydrochloride
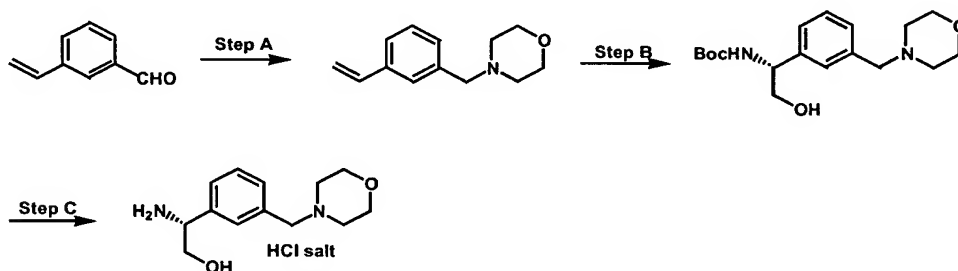
20

Step A: 4-(3-Vinyl-benzyl)-morpholine

        To the solution of 3-vinyl benzaldehyde (5 g, 38 mmol) and morpholine
(3.0 mL, 52 mmol) in dichloromethane (126ml) was added sodium
25 triacetoxyborohydride (19.2 g, 92 mmol) in portion at 0°C followed by acetic acid
(2.3 mL, 40 mmol). After the addition, reaction mixture was raised to room
temperature and stirred at room temperature overnight. The reaction mixture was
diluted with dichloromethane washed with 1N NaOH and extracted with

dichloromethane 3 times. The combined organic layer was dried over magnesium sulfate and concentrated under vacuum to give the title compound as pale yellow oil (7.2 g, 93% yield)

5   ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.18-7.35 (m, 4 H), 6.70 (dd, J = 11, 18Hz, 1 H), 5.75 (d, J = 18, 1H), 5.24 (d, J = 11, 1H), 3.71 (t, J = 5 Hz, 4H), 3.50 (s, 2H), 2.45 (t, J = 5 Hz, 4H).

Step B: (R)- [2-Hydroxy-1-(3-morpholin-4-ylmethyl-phenyl)-ethyl]-carbamic
10   acid tert-butyl ester

Sodium hydroxide (3.13g, 78mmol) was dissolved in water (190 mL) and 9 mL of this solution was used to dissolve potassium osmium (VI) oxide dihydrate (387 mg, 4 mol%) to get a purple suspension. The rest of the sodium hydroxide solution was treated with t-butyl carbamate (9.16 g, 78 mmol) in n-
15   propanol (89 mL), followed by addition of t-butyl hypochlorite (8.86 mL, 78 mmol). This solution was stirred for 5 minutes at 0°C, then hydroquinidine 1,4-phthalazinediyl diether (1.22 g, 6 mol%) in n-propanol (89 mL) was added, followed by solution of 4-(3-vinyl-benzyl)-morpholine (5.3 g, 26 mmol) in n-propanol (89 mL) and solution of potassium osmium (VI) oxide dihydrate
20   previously made. The reaction mixture was stirred at 0°C for 20 min. The reaction mixture was diluted with saturated sodium sulfite solution and the organic layer was separated. The aqueous layer was extracted with dichloromethane twice. The combined organic layer was dried over magnesium sulfate, concentrated under vacuum. The crude product was purified by flash
25   chromatography with gradient from 35% acetone/hexanes to 45% acetone/hexanes over 20 min. to afford the title compound as a sticky oil (2.1 g, 24% yield).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.17-7.31 (m, 4H), 5.30 (d, J = 7, 1H), 4.75 (s,
30   1H), 3.85 (m, 2H), 3.69 (t, J = 5 Hz, 4H), 3.48 (s, 2H), 2.43 (t, J = 5 Hz, 4H), 1.43 (s, 9H).
MS (M+H)$^+$ 337

Step C: _(R)- 2-Amino-2-(3-morpholin-4-ylmethyl-phenyl)-ethanol hydrochloride_

(R)- [2-Hydroxy-1-(3-morpholin-4-ylmethyl-phenyl)-ethyl]-carbamic acid tert-butyl ester (2.1 g, 6.25 mmol) in methanol (22 mL) was added hydrochloric acid (2.0M in ethyl ether) (10.88 mL, 21.8 mmol) and reaction mixture was

5   stirred at room temperature for 5hr. The reaction mixture was concentrated under vacuum to provide the title compound as a pale green solid (quantitative yield).

^{1}H NMR (400 MHz, CD$_3$OD): δ 7.70 (s, 1H), 7.57-7.62 (m, 3H), 4.41 (m, 3H), 3.78-4.10 (m, 6H), 3.18-3.39 (m, 4H).

10   MS (M+H)$^+$ 237

Preparation 2

Preparation of (R)-2-Amino-2-(3-morpholin-4-yl-phenyl)-ethanol hydrochloride

15
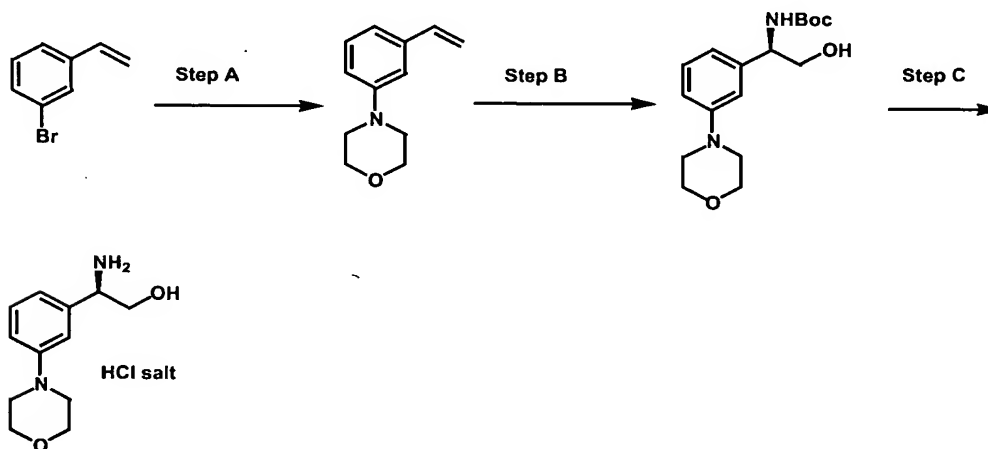
Step A: _4-(3-Vinyl-phenyl)-morpholine_

Mixture of 3-bromo-styrene (11.2 g, 61.2 mmol), morpholine (123 mL), palladium acetate (343 mg, 2.5mol%), di-t-butyl-biphenylphosphine (911 mg, 5

20   mol%), sodium _t_-butyloxide (6.47 g, 67.4 mmol) was stirred at 80°C in a sealed tube for 30 minutes. After cooling down, the reaction mixture was diluted with dichloromethane (250 mL) and washed with water (100 mL). The aqueous layer was extracted with dichloromethane (2x125 mL) and the combined organic layer was dried over magnesium sulfate and concentrated under vacuum. The crude

product was purified by Flash Chromatography of Biotage with 30% Ethyl Acetate/Hexanes. The title compound was obtained as pale yellow clear oil (10.7 g, 93% yield).

5   ^{1}H NMR (CDCl$_3$): 3.18 (m, 4H), 3.87 (m, 4H), 5.23 (d, 1H), 5.73 (d, 1H), 6.69 (dd, 1H), 6.84 (m, 1H), 6.96 (m, 2H), 7.25 (m, 1H).
MS (M+H)$^+$ 190

Step B: [(R)-2-Hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-carbamic acid tert-
10   butyl ester

Sodium hydroxide (275 mg, 6.88 mmol) was dissolved in water (38.2 mL) and 1.8 mL of this solution was used to dissolve potassium osmium (VI) oxide dihydrate (80 mg, 4 mol%) to get a purple suspension. The rest of the sodium hydroxide solution was treated with t-butyl carbamate (1.86 g, 15.9 mmol) in
15   n-propanol (21 mL), followed by addition of t-butyl hypochlorite (1.8 mL, 15.7 mmol). This solution was stirred for 5 minutes then hydroquinidine 1,4-phthalazinediyl diether (210 mg, 5 mol%) in n-propanol (18 mL) was added, followed by solution of 4-(3-vinyl-phenyl)-morpholine (1 g, 5.3 mmol) in n-propanol (18 mL) and solution of potassium osmium (VI) oxide dihydrate
20   previously made. The reaction mixture was stirred at room temperature for 1hr. The reaction mixture was diluted with water (50 mL), extracted with dichloromethane (3x200 mL). The combined organic layer was dried over magnesium sulfate, concentrated under vacuum. The crude product was purified by flash chromatography with 30% acetone/hexanes twice and 25%
25   acetone/hexanes once to afford the title compound as a white solid (810 mg, 48% yield).

^{1}H NMR (CDCl$_3$): 1.43 (broad s, 9H), 3.16 (m, 4H), 3.84 (m, 4H), 4.71 (broad s, 1H), 5.22 (broad d, 1H), 6.83 (m, 3H), 7.25 (m, 1H).
30   MS (M+H)$^+$ 323

Step C: (R)-2-Amino-2-(3-morpholin-4-yl-phenyl)-ethanol hydrochloride

(R)-2-Hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (500mg, 1.55 mmol) in methanol (3.1 mL) was added hydrochloric acid (1.0 M in ethyl ether) (4.65 mL, 4.65 mmol) and reaction mixture was stirred at room temperature for 24hrs. The reaction mixture was concentrated under vacuum to provide the title compound as yellow solid (457 mg, quantitative yield) ready for next step without any further purification.

MS $(M+H)^+$ 223.

Preparation 3

Preparation of (R)-2-Amino-2-(4-fluoro-3-morpholin-4-yl-phenyl)-ethanol
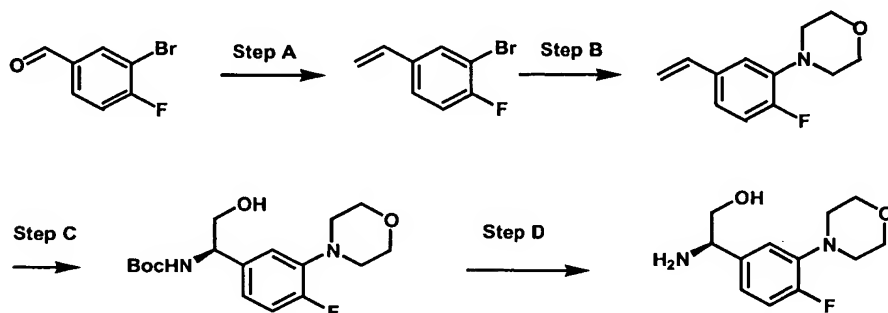
Step A: 2-Bromo-1-fluoro-4-vinyl-benzene

To a suspension of Ph_3PCH_3Br (57 g) in THF (240 mL) at 0° C was dropwise added *n*-BuLi (1.6 N, 100 mL). The resulting mixture was allowed to warm to room temperature and stirred for 1 h. After recooling to 0° C, a solution of 3-bromo-4-fluoro-benzaldehyde (20.3 g) in THF (20 mL) was added. The resulting mixture was allowed to warm to room temperature and stirred for 1h. The reaction mixture was quenched with water, concentrated, and extracted with methylene chloride. The combined organic layer was dried over magnesium sulfate, concentrated under vacuum. The crude product was purified by flash chromatography eluting with 10% ethyl acetate in hexanes to give the title compound as an oil (18 g).

^{1}H NMR (CDCl$_3$): δ 7.59-7.56 (m, 1 H), 7.31-7.27 (m, 1 H), 7.05 (t, J = 8.4 Hz, 1 H), 6.65 (dd, J = 17.7, 11.1 Hz, 1 H), 6.55 (d, J = 17.4 Hz, 1 H), 5.28 (d, J = 10.8 Hz, 1 H).

Step B: 4-(2-Fluoro-5-vinyl-phenyl)-morpholine

A mixture of 2-Bromo-1-fluoro-4-vinyl-benzene(8 g), morpholine (20 mL), Pd$_2$(dba)$_3$ (1.83 g), di-*t*-butyl-biphenylphosphine (1.2 g), K$_3$PO$_4$ (17 g) in DME (60 mL) was stirred at reflux for 4 h. The reaction mixture was cooled down to room temperature, diluted with methylene chloride, and filtered. The filtrate was concentrated *in vacuo*. The crude product was purified by Flash Chromatography of Biotage eluting with 7% ethyl acetate in hexanes to give the title compound as an oil (5 g).

^{1}H NMR (CDCl$_3$): δ 7.24-6.93 (m, 3 H), 6.68 (dd, J = 17.7, 10.8 Hz, 1 H), 5.66 (d, J = 17.4 Hz, 1 H), 5.22 (d, J = 10.8 Hz, 1 H). 3.88 (m, 4H), 3.10 (m, 4H). MS (M+H)$^+$ 208.

Step C: (*R*)-4-of [1-(Fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-carbamic acid *tert*-butyl ester

Sodium hydroxide (3.6 g) was dissolved in water (220 mL) and 10 mL of this solution was used to dissolve potassium osmium (VI) oxide dihydrate (434 mg) to get a purple suspension. The rest of the sodium hydroxide solution was treated with *t*-butyl carbamate (10.666 g) in *n*-propanol (120 mL), followed by addition of *t*-butyl hypochlorite (11 mL). This solution was stirred for 5 min, then hydroquinidine 1,4-phthalazinediyl diether (1466 mg) in *n*-propanol (120 mL) was added, followed by a solution of 4-(2-Fluoro-5-vinyl-phenyl)-morpholine (5 g) in *n*-propanol (206 mL) and a solution of potassium osmium (VI) oxide dihydrate previously made. The reaction mixture was stirred at room temperature for 0.5 h. The reaction mixture was quenched with saturated Na$_2$SO$_3$ solution. After concentration, the residue was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, concentrated under vacuum. The crude product was purified by flash

chromatography eluting with 33% ethyl acetate in hexanes to give the title compound as a solid (2.2 g).

^{1}H NMR (CDCl$_3$): δ 7.03-6.83 (m,3 H), 5.19 (br s, 1 H0, 4.68 (br s, 1 H), 3.87 (m, 6 H), 3.09 (m, 4 H), 1.44 (s, 9 H).
MS (M+H)$^+$ 341.

Step D: <u>(R)-2-Amino-2-(4-fluoro-3-morpholin-4-yl-phenyl)-ethanol</u>

A solution of TFA (5 mL) and (R)-[1-(fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-carbamic acid *tert*-butyl ester(1.2 g) in methylene chloride (15 mL) was stirred for 2 h. After concentration, the residue was neutralized with 10 N NaOH and extracted with methylene chloride. The organic layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo to give the title compound as a solid (720 mg).

^{1}H NMR (CDCl$_3$): δ 7.07-6.87 (m, 3 H), 4.04-4.00 (m, 1 H), 3.87-3.84 (m, 4 H), 3.73-3.68 (m, 1 H), 3.55-3.52 (m, 1 H), 3.09 –3.06 (m, 4 H).
MS (M+H)$^+$ 241.

<u>Preparation 4</u>
<u>Preparation of (R)-2-Amino-2-naphthalen-2-yl-ethanol hydrochloride</u>
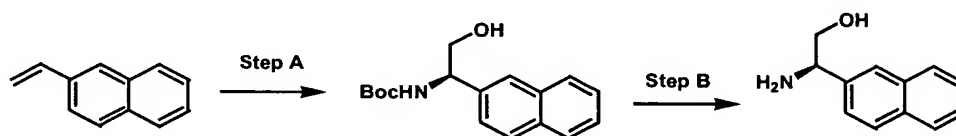
Step A: <u>(R)-(2-Hydroxy-1-naphthalen-2-yl-ethyl)-carbamic acid tert-butyl ester</u>

Sodium hydroxide (1.89 g, 16 mmol) was dissolved in water (115 mL) and 5.4 mL of this solution was used to dissolve potassium osmium (VI) oxide dihydrate (240 mg) to get a purple suspension. The rest of the sodium hydroxide solution was treated with *t*-butyl carbamate (5.580 g, 47.1 mmol) in *n*-propanol (54 mL), followed by addition of *t*-butyl hypochlorite (5.4 mL, 47.1 mmol). This

solution was stirred for 5 min, then hydroquinidine 1,4-phthalazinediyl diether
(630 mg) in n-propanol (54 mL) was added, followed by a solution of 2-
vinylnaphthalene (2.5 g, 16 mmol) in n-propanol (54 mL) and a solution of
potassium osmium (VI) oxide dihydrate previously made. The reaction mixture
5 was stirred at room temperature for 0.5 hr. The reaction mixture was quenched
with saturated $NaHSO_3$ solution. After concentration, the residue was extracted
with ethyl acetate. The combined organic layer was dried over magnesium
sulfate, concentrated under vacuum. The crude product was purified by flash
chromatography with 20% ethyl acetate in hexanes to give the title compound
10 (2.6 g) as a solid.

^{1}H NMR ($CDCl_3$): δ 7.83-7.74 (m, 4 H), 7.47-7.37 (m, 3 H), 5.39 (br s, 1 H),
4.91 (br s, 1 H), 3.90 (d, $J = 3.9$ Hz, 2 H), 1.44 (s, 9 H).
MS $(M+H)^+$ 288.

15

Step B: (R)-2-Amino-2-naphthalen-2-yl-ethanol hydrochloride

(R)-(2-Hydroxy-1-naphthalen-2-yl-ethyl)-carbamic acid *tert*-butyl ester
(2.5 g) and 9 mL of 4 N HCl in ethyl acetate at 50° C was stirred for 2 h. After
concentration, the residue was neutralized with 10 N NaOH and extracted with
20 methylene chloride. The organic layer was washed with brine, dried over
Na_2SO_4, and concentrated to give the title compound (1.2 g) as a solid which
was used in the next step without further purification.
MS $(M+H)^+$ 188.

25   Preparation 5
Preparation of (R)-2-Amino-2-(7-methoxy-naphthalen-2-yl)-ethanol
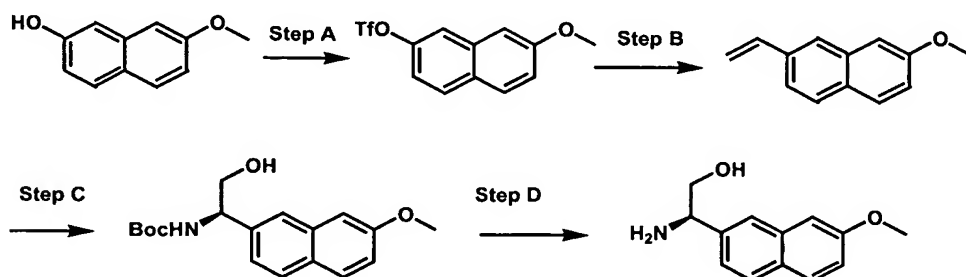
Step A: Trifluoro-methanesulfonic acid 7-methoxy-naphthalen-2-yl ester

    To a solution of 7-methoxy-naphthalen-2-ol (17.4 g) and pyridine (40 mL) in methylene chloride (150 mL) at 0°C was added a solution of trifluoromethanesulfonic anhydride (32.4 g) in CH_2Cl_2 (15 mL). After stirring for
5   0.5 h, the reaction mixture was warmed to rt and stirred for 1 h. The reaction was quenched with water carefully. The organic layer was washed with 10% H_3PO_4, dried over $MgSO_4$. After concentration, the crude product was purified by flash chromatography eluting with 20% ethyl acetate in hexanes to give the title compound as an oil (28 g).
10

^{1}H NMR (CDCl$_3$): δ 7.83-7.74 (m,2 H), 7.63 (d, J = 2.4 Hz, 1 H), 7.24-7.12 (m, 3 H), 3.92 (s, 3 H).

Step B: 2-Methoxy-7-vinyl-naphthalene
15   To a mixture of (Ph$_3$P)$_2$PdCl$_2$ (1.752 g), LiCl (6.36 g), and trifluoro-methanesulfonic acid 7-methoxy-naphthalen-2-yl ester (15.3 g) was added dropwise tributyl(vinyl)tin (19.02 g). The resulting mixture was stirred over 4 h at 90°C. The reaction was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with water and dried over $MgSO_4$. After concentration,
20   the crude product was purified by flash chromatography eluting with 20% ethyl acetate in hexanes to give the title compound as an oil (9 g).

^{1}H NMR (CDCl$_3$): δ 7.72-7.65 (m,2 H), 7.49 (dd, J = 8.7, 1.8 Hz, 1 H), 7.11-7.08 (m, 3 H), 6.90 (dd, J = 17.4, 10.8 Hz, 1H), 5.88 (d, J = 17.7 Hz, 1 H), 5.33 (d, J =
25   10.8 Hz, 1 H), 3.92 (s, 3 H).
MS (M+H)$^+$ 185.

Step C: (R)-[2-Hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-carbamic acid tert-butyl ester
30   Sodium hydroxide (1.8 g) was dissolved in water (110 mL) and 5 mL of this solution was used to dissolve potassium osmium (VI) oxide dihydrate (217 mg) to get a purple suspension. The rest of the sodium hydroxide solution was

treated with t-butyl carbamate (5.333 g) in *n*-propanol (60 mL), followed by

addition of *t*-butyl hypochlorite (5.5 mL). This solution was stirred for 5 min,

then hydroquinidine 1,4-phthalazinediyl diether (733 mg) in *n*-propanol (60 mL)

was added, followed by a solution of 2-methoxy-7-vinyl-naphthalene (2 g) in *n*-

5   propanol (103 mL) and a solution of potassium osmium (VI) oxide dihydrate

previously made. The reaction mixture was stirred at room temperature for 0.5 h.

The reaction mixture was quenched with saturated Na_2SO_3 solution. After

concentration, the residue was extracted with ethyl acetate. The combined

organic layers were dried over magnesium sulfate and concentrated under

10   vacuum. The crude product was purified by flash chromatography eluting with

33% ethyl acetate in hexanes to give the title compound as a solid (1.585 g).

Step D: (*R*)-2-Amino-2-(7-methoxy-naphthalen-2-yl)-ethanol

         A solution of TFA (8 mL) and (*R*)-[2-hydroxy-1-(7-methoxy-naphthalen-

15   2-yl)-ethyl]-carbamic acid *tert*-butyl ester (1.268 g) in methylene chloride (24

mL) was stirred for 2 h. After concentration, the residue was neutralized with 10

N NaOH and extracted with methylene chloride. The organic layer was washed

with brine, dried over Na_2SO_4, and concentrated to give the title compound as a

solid (860 mg).

20

Preparation 6

Preparation of (3R,2S)-3-Amino-3-naphthalen-2-yl-propane-1,2-diol
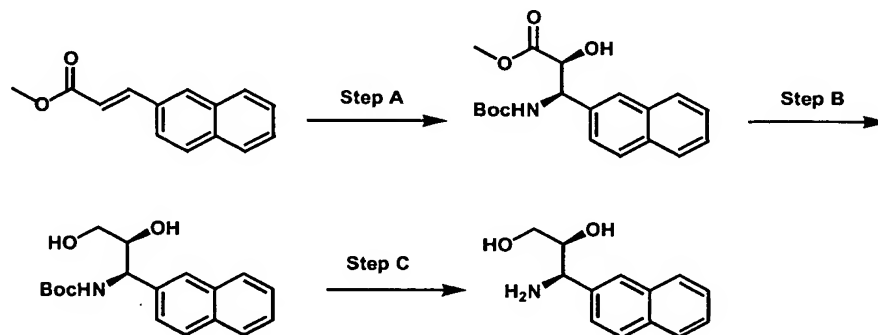
25

Step A: (1*R*, 2*S*)-3-*tert*-Butoxycarbonylamino-2-hydroxy-3-naphthalen-2-yl-propionic acid methyl ester

Sodium hydroxide (3.6 g) was dissolved in water (220 mL) and 10 mL of this solution was used to dissolve potassium osmium (VI) oxide dihydrate (2434 mg) to get a purple suspension. The rest of the sodium hydroxide solution was treated with *t*-butyl carbamate (10.666 g) in *n*-propanol (120 mL), followed by addition of *t*-butyl hypochlorite (11 mL). This solution was stirred for 5 min, then hydroquinidine 1,4-phthalazinediyl diether (1466 mg) in *n*-propanol (120 mL) was added, followed by a solution of 3-naphthalen-2-yl-acrylic acid methyl ester (5 g) in *n*-propanol (206 mL) and a solution of potassium osmium (VI) oxide dihydrate previously made. The reaction mixture was stirred at room temperature for 0.5 h. The reaction mixture was quenched with saturated $NaHSO_3$ solution. After concentration, the residue was extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate, concentrated under vacuum. The crude product was purified by flash chromatography with 33% ethyl acetate in hexanes to give the title compound (7.3 g) as a solid.

^{1}H NMR ($CDCl_3$): δ 7.84-7.79 (m, 4 H), 7.50-7.43 (m, 3 H), 5.53 (d, J = 8.8 Hz, 1 H), 45.38 (d, J = 8.8 Hz, 1 H), 4.56 (br s, 1 H), 3.85 (s, 3 H), 3.22 (br s, 1 H), 1.44 (s, 9 H).

Step B: (1*R*,2*S*)-(2,3-Dihydroxy-1-naphthalen-2-yl-propyl)-carbamic acid *tert*-butyl ester

To a solution of (1*R*, 2*S*)-3-*tert*-butoxycarbonylamino-2-hydroxy-3-naphthalen-2-yl-propionic acid methyl ester (345 mg) and MeOH (96 mg) in ether (10 mL) was added $LiBH_4$ (88 mg). The resulting mixture was refluxed for 0.5 h. After cooling to room temperature, the reaction mixture was quenched with 1 N HCl. The organic layer was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 33% ethyl acetate in hexanes to give the title compound as a solid (100 mg).

^{1}H NMR (CDCl$_3$): δ 7.84-7.76 (m, 4 H), 7.48-7.40 (m, 3 H), 5.44 (br s, 1 H), 4.98 (br s, 1 H), 4.10 (br s, 1 H), 3.59 (d, J = 6 Hz, 2 H), 1.44 (s, 9 H).

MS (M+H)$^+$ 318.

5 Step C: (3R,2S)-3-Amino-3-naphthalen-2-yl-propane-1,2-diol

A solution of TFA (5 mL) and (1R,2S)-(2,3-dihydroxy-1-naphthalen-2-yl-propyl)-carbamic acid *tert*-butyl ester (1.72 g) in methylene chloride (15 mL) was stirred for 2 h. After concentration, the residue was neutralized with 10 N NaOH and extracted with methylene chloride. The combined organic layer was washed

10 with brine, dried over Na$_2$SO$_4$, and concentrated *in vacuo* to give the title compound as a solid (1.1 g).

^{1}H NMR (CDCl$_3$): δ 7.83-7.75 (m, 4 H), 7.48-7.44 (m, 3 H), 4.09 (d, J = 7 Hz, 1 H), 3.82-3.79 (m, 1H), 3.64 (dd, J = 11.5, 3 Hz, 1 H), 3.53 (dd, J = 11.5, 4.5 Hz, 1

15 H).

MS (M+H)$^+$ 218.

<div align="center">

Preparation 7

Preparation of 2-Amino-2-(3-pyridin-3-yl-phenyl)-ethanol

</div>

20
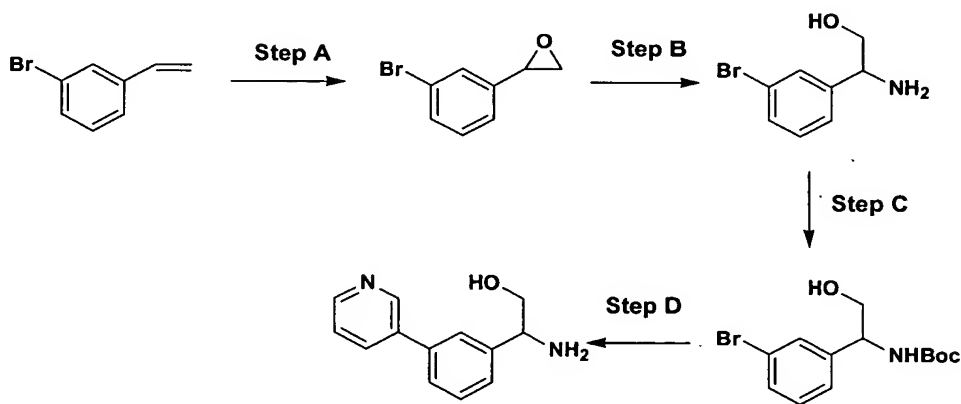
Step A: 2-(3-Bromo-phenyl)-oxirane

1-Bromo-3-vinyl-benzene (5g, 27.3 mmol) and 3-cyanopyridine (551mg,

25 2.7 mmol) were added in CH$_2$Cl$_2$ (25 mL), Methyltrioxorhenium (VII) (34 mg,

0.137mmol) and hydrogen peroxide (30%) (6.2 mL, 54.6 mmol) were added and the reaction mixture was stirred at room temperaute for 18 h. Sodium sulfite 1M (10 mL) and saturated sodium bicarbonate were added, the aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over anhydrous magnesium sulfate, filtered. The filtrate was concentrated *in vacuo* to provide the title compound as clear oil ((5.05g, 93 %).

^{1}H NMR (CDCl$_3$): δ 2.75 (dd, J = 2.5, 5.3 Hz,1 H), 3.14 (dd, J = 4.0, 5.5 Hz,1 H), 3.82 (dd, J = 2.5, 4.0 Hz,1 H), 7.15-7.25 (m, 2 H), 7.35-7.45 (m, 2 H).

Step B: <u>2-Amino-2-(3-bromo-phenyl)-ethanol</u>

To a solution of 2-(3-bromo-phenyl)-oxirane (2.5g, 12.6 mmol) in CH_2Cl_2 (20 mL) was added azidotrimethylsilane (2.5 mL, 18.84 mmol), followed by aluminium isopropoxide (256 mg, 1.26mmol) . The reaction mixture was stirred at room temperature for 18 h. Sodium potassium tartrate 1M (30 mL) was added, the aqueous layer was extracted with CH_2Cl_2, and the organic layers were dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated *in vacuo*, and the crude compound is purified by flash chromatography (10% EtOAc/Hex) to provide 2-azido-2-(3-bromo-phenyl)-ethanol (876 mg, 29 %). To a solution of 2-azido-2-(3-bromo-phenyl)-ethanol (876 mg) in THF (10 mL) was added polymer supported triphenylphosphine (3 mmol/g) (2 g, 6 mmol), and the mixture was heated to 60°C for 30 min. The polymer was then filtered and washed with CH_2Cl_2. The polymer was suspended in THF (20 mL) and concentrated NH$_4$OH (10 mL) was added, and this mixture was agitated for 24 h. The polymer was filtered and the liquid phase was evaporated *in vacuo* to afford the title compound (110 mg, 14%).

^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.75 (dd, J = 2.5, 5.3 Hz,1 H), 3.14 (dd, J = 4.0, 5.5 Hz,1 H), 3.82 (dd, J = 2.5, 4.0 Hz,1 H), 7.15-7.25 (m, 2 H), 7.35-7.45 (m, 2 H).

Step C: [1-(3-Bromo-phenyl)-2-hydroxy-ethyl]-carbamic acid *tert*-butyl ester

　　　　To a solution of 2-amino-2-(3-bromo-phenyl)-ethanol (110 mg, 0.51 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (71 µL, 0.51 mmol), di-*tert*-butyl dicarbonate (111 mg, 0.51 mmol), and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was washed with saturated NH_4Cl (20 mL), and the organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* to provide the title compound as a white solid.

Step D: 2-Amino-2-(3-pyridin-3-yl-phenyl)-ethanol

　　　　To a solution of [1-(3-bromo-phenyl)-2-hydroxy-ethyl]-carbamic acid *tert*-butyl ester (160 mg, 0.51 mmol) in ethyleneglycoldimethylether (10 mL) in a sealed tube were added pyridine-3-boronic acid (82 mg, 0.66 mmol), cesium carbonate (500 mg, 1.53 mmol) and water (2mL). Argon was bubbled through the solution for 10 min, and $Pd(PPh_3)_4$ (30 mg, 0.025 mmol) was added. The reaction mixture was heated at 100°C for 6 h. The reaction mixture was cooled down to room temperature, and ethyl acetate (20 mL) was added. The reaction mixture was washed with saturated NH_4Cl (2x10 mL), and the organic layer was dried over anhydrous magnesium sulfate, filtered. The filtrate was concentrated *in vacuo*, and the crude product was diluted in CH_2Cl_2 (8 mL) and trifluoroacetic acid (2 mL). The reaction mixture was agitated for 1 h and concentrated *in vacuo*. The residue was purified by solid phase extraction (SCX cartridge, silca gel benzene sulfonic acid linked) to give the title product (110mg, 100% yield) as brown oil.

^{1}H NMR (DMSO d_6): δ 1.28 (d, 3 H, J = 6.8 Hz), 4.04 (q, 1 H, J = 6.8 Hz), 7.4-7.45 (m, 2H), 7.5-7.55 (m, 1H), 7.61 (d, 1H J = 7.8 Hz,), 7.72 (s, 1H), 8.15 (dd, 1H, J = 8.3, 2.5 Hz,), 8.73 (d, 1H, J = 3.3 Hz).

EXAMPLES

EXAMPLE 1

(*R*)- 3-(2-Fluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-ylmethyl-phenyl)-
ethyl]-acrylamide TFA salt
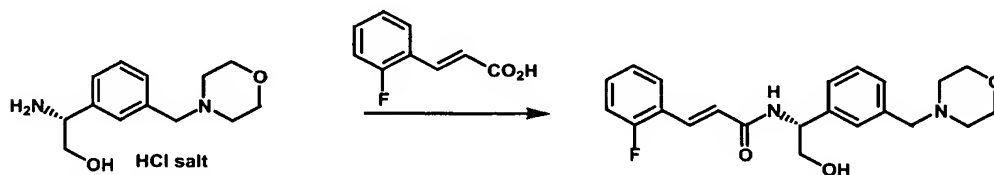
Mixture of (*R*)- 2-Amino-2-(3-morpholin-4-ylmethyl-phenyl)-ethanol
hydrochloride (30 mg, 0.10 mmol), 2-fluorocinnamic acid (15.3 mg, 0.10 mmol),
benzotriazol-1-yloxytris(pyrrolidino) phosphonium hexafluorophosphate (50 mg,
0.10 mmol) and triethylamine (0.05 mL, 0.40mmol) in DMF (0.5 ml) was stirred
at room temperature for 3 h. The reaction mixture was diluted with methanol and
purified by prep HPLC. The title compound was obtained as pale yellow sticky
oil.

HPLC rt: 1.05 min (method d)
^{1}H NMR (500 MHz, CD$_3$OD): δ 7.69-7.62 (m, 2H), 7.55-7.49 (m, 3H), 7.43-7.39
(m, 2H), 7.25-7.14 (m, 2H), 6.85 (d, J=15, 1H), 5.10 (t, J=5, 1H), 4.37 (d, J=5,
2H), 4.11-3.97 (m, 2H), 3.84 (d, J=10, 2H), 3.77-3.65 (m, 2H), 3.45-3.14 (m,
4H).
MS (M+H)$^+$ 385

EXAMPLES 2 - 13

Examples 2 - 13 were prepared from the appropriate corresponding acids
using the same general procedure as described in Example 1.

Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass $(M+H)^+$ m/z
2		(*R*)- 3-(3-Fluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-ylmethyl-phenyl)-ethyl]-acrylamide	1.21(a)	385
3		(*R*)- 3-(4-Fluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-ylmethyl-phenyl)-ethyl]-acrylamide	1.18 (a)	385
4		(*R*)- 3-(2,4-Difluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-ylmethyl-phenyl)-ethyl]-acrylamide	1.24 (a)	403
5		(*R*)- 3-(2,3-Difluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-ylmethyl-phenyl)-ethyl]-acrylamide	1.24 (a)	403
6		(*R*)- 3-(2,5-Difluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-ylmethyl-phenyl)-ethyl]-acrylamide	1.20 (a)	403
7		(*R*)- 3-(2,6-Difluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-ylmethyl-phenyl)-ethyl]-acrylamide	1.16 (a)	403
8		(*R*)- 3-(3,4-Difluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-ylmethyl-phenyl)-ethyl]-acrylamide	1.25 (a)	403
9		(*R*)- 3-(2-Chloro-4-fluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-ylmethyl-phenyl)-ethyl]-acrylamide	1.37 (a)	419

Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass (M+H)$^+$ m/z
10		(R)- 3-(4-Chloro-2-fluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-ylmethyl-phenyl)-ethyl]-acrylamide	1.41 (a)	419
11		(R)- N-[2-Hydroxy-1-(3-morpholin-4-ylmethyl-phenyl)-ethyl]-3-thiophen-3-yl-acrylamide	1.01 (a)	373
12		(R)- N-[2-Hydroxy-1-(3-morpholin-4-ylmethyl-phenyl)-ethyl]-3-thiophen-2-yl-acrylamide	1.02 (a)	373
13		(R)- 3-Furan-2-yl-N-[2-hydroxy-1-(3-morpholin-4-ylmethyl-phenyl)-ethyl]-acrylamide	0.88 (a)	357

EXAMPLE 14

(R)-N-[2-Hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-3-phenyl-acrylamide

5
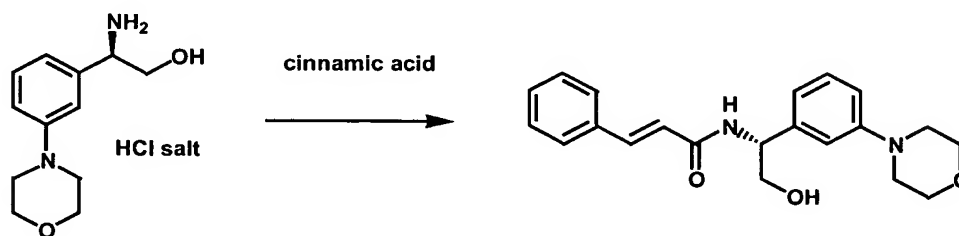
Mixture of (R)-2-Amino-2-(3-morpholin-4-yl-phenyl)-ethanol hydrochloride (70 mg, 0.24 mmol), cinnamic acid (35 mg, 0.24 mmol), EDC (91 10   mg, 0.47 mmol), DMAP (29 mg, 0.24 mmol), triethyl amine (0.13 mL, 0.95 mmol) in dichloromethane (1 mL) was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and purified by flash

chromatography with 60% acetone/hexanes to provide the title compound as a white solid (57mg, 68%yield).

HPLC rt: 1.14 min (method c)

5   ^{1}H NMR (CDCl$_3$): δ 3.23 (m, 4H), 3.97 (m, 6H), 5.18 (m, 1H), 6.48 (m, 2H), 7.10(m, 3H), 7.30 (m, 3H), 7.50 (m, 2H), 7.69 (d, 1H).

MS (M+H)$^+$ 353.

EXAMPLES 15 - 29

10   Examples 15 - 29 were prepared from the appropriate corresponding acid using the same general procedure as described in Example 14.

Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass (M+H)$^+$ m/z
15		(R)- N-[2-Hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-3-phenyl-propionamide	1.26 (b)	355
16		(R)- 3-(2-Fluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide	1.38(b)	371
17		(R)- 3-(3-Fluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide	1.40 (b)	371
18		(R)- 3-(2,4-Difluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide	1.46 (b)	389
19		(R)- 3-(2,3-Difluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide	1.48 (b)	389

Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass (M+H)⁺ m/z
20		(R)- 3-(2,5-Difluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide	1.44 (b)	389
21		(R)- 3-(3,5-Difluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide	1.49 (b)	389
22		(R)- 3-(2-Chloro-4-fluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide	1.59 (b)	405
23		(R)- 3-(2-Chloro-6-fluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide	1.32 (c)	405
24		(R)- N-[2-Hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-3-(4-trifluoromethyl-phenyl)-propionamide	1.47 (c)	421
25		(R)- 3-(2,6-Difluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide	1.40 (b)	389
26		(R)- 3-(4-Chloro-2-fluoro-phenyl)-N-[2-hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide	1.44 (c)	405
27		(R)- N-[2-Hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-3-p-tolyl-acrylamide	1.30 (c)	367

Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass (M+H)+ m/z
28		(R)- N-[2-Hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-3-m-tolyl-acrylamide	1.31 (c)	367
29		(R)- N-[2-Hydroxy-1-(3-morpholin-4-yl-phenyl)-ethyl]-3-o-tolyl-acrylamide	1.28 (c)	367

EXAMPLE 30

(R)-3-(2-Chloro-phenyl)-N-[1-(4-fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-

5   ethyl]-acrylamide

A mixture of (R)-2-amino-2-(4-fluoro-3-morpholin-4-yl-phenyl)-ethanol

10   (0.1 mmol), 2-chloro-cinnamic acid (0.1 mmol), EDC•HCl (0.2 mmol), DMAP

(0.1 mmol), triethyl amine (0.3 mmol) in dichloromethane (2 mL) was stirred at

room temperature for 14 h. The reaction mixture was purified by flash

chromatography with 5% methnol in ethyl acetate to provide the title compound

as a solid (29 mg).

15

HPLC rt: 1.48 min (method d)

^{1}H NMR (CDCl$_3$): δ 8.01 (d, J = 15.5 Hz, 1 H), 7.49-6.87 (m, 7 H),6.50 (d, J =

15.5 Hz, 1 H), 5.13-5.07 (m, 1 H), 3.90-3.80 (m, 6 H), 3.06-3.03 (m, 4 H).
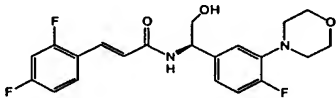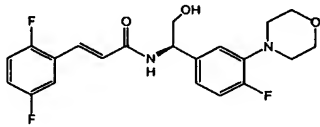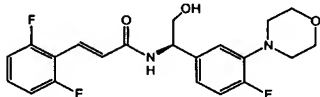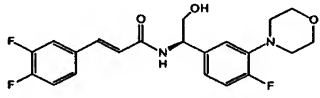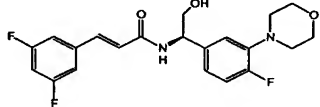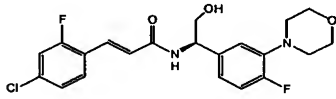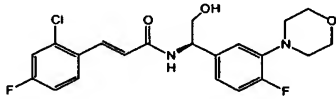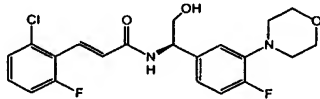
MS (M+H)+ 405.

20

EXAMPLES 31 - 45

Examples 31 - 45 were prepared from the appropriate corresponding acid using the same general procedure as described in Example 30.

Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass (M+H)$^+$ m/z
31		(R)- N-[1-(4-Fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-3-(2-fluoro-phenyl)-acrylamide	1.39 (d)	389
32		(R)- N-[1-(4-Fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-3-(3-fluoro-phenyl)-acrylamide	1.39 (c)	389
33		(R)- N-[1-(4-Fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-3-(4-fluoro-phenyl)-acrylamide	1.39 (d)	389
34		(R)- N-[1-(4-Fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-3-phenyl-acrylamide	1.35 (d)	371
35		(R)- 3-(4-Chloro-phenyl)-N-[1-(4-fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-acrylamide	1.53 (d)	405
36		(R)- N-[1-(4-Fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-3-o-tolyl-acrylamide	1.46 (d)	385
37		(R)- N-[1-(4-Fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-3-p-tolyl-acrylamide	1.49 (d)	385

Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass (M+H)$^+$ m/z
38		(*R*)- 3-(2,4-Difluoro-phenyl)-N-[1-(4-fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-acrylamide	1.50 (d)	407
39		(*R*)- 3-(2,5-Difluoro-phenyl)-N-[1-(4-fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-acrylamide	1.42 (d)	407
40		(*R*)- 3-(2,6-Difluoro-phenyl)-N-[1-(4-fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-acrylamide	1.40 (d)	407
41		(*R*)- 3-(3,4-Difluoro-phenyl)-N-[1-(4-fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-acrylamide	1.45 (d)	407
42		(*R*)- 3-(3,5-Difluoro-phenyl)-N-[1-(4-fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-acrylamide	1.42 (d)	407
43		(*R*)- 3-(4-Chloro-2-fluoro-phenyl)-N-[1-(4-fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-acrylamide	1.52 (d)	423
44		(*R*)- 3-(2-Chloro-4-fluoro-phenyl)-N-[1-(4-fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-acrylamide	1.49 (d)	423
45		(*R*)- 3-(2-Chloro-6-fluoro-phenyl)-N-[1-(4-fluoro-3-morpholin-4-yl-phenyl)-2-hydroxy-ethyl]-acrylamide	1.43 (d)	423

EXAMPLE 46

(R)- 3-(2-Fluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide
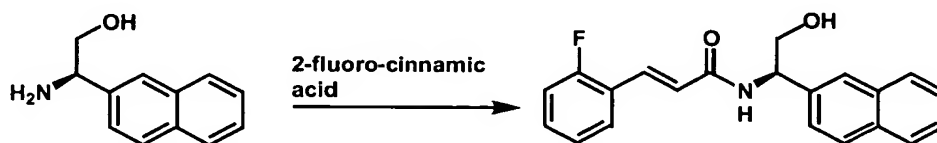
5

A mixture of (R)-2-amino-2-naphthalen-2-yl-ethanol (0.2 mmol), 2-fluorocinnamic acid (0.2 mmol), EDC HCl (0.4 mmol), DMAP (0.2 mmol), triethyl amine (0.6 mmol) in dichloromethane (4 mL) was stirred at room temperature for 14 h. The reaction mixture was purified by flash chromatography
10 with 50% ethyl acetate in hexanes to provide the desired product (56 mg) as a solid.

HPLC rt: 1.43 (method d)

^{1}H NMR (CD$_3$OD): δ 7.86-7.43 (m, 10 H), 7.22-7.15 (m, 2 H), 6.92 (d, $J = 15.9$
15 Hz, 1 H), 5.31 (t, $J = 6.9$ Hz, 1 H), 3,98 (m, 2 H).

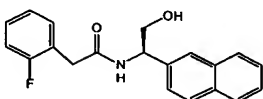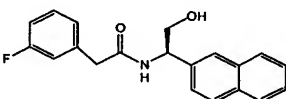MS (M+H)$^+$ 336.

EXAMPLES 47 - 91
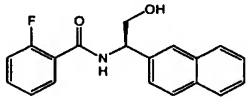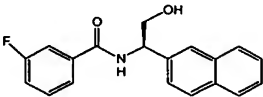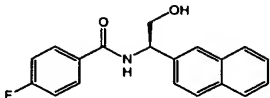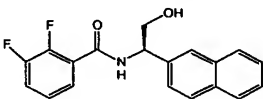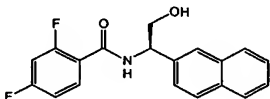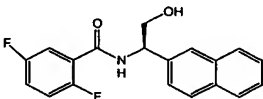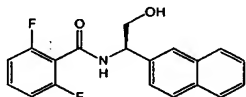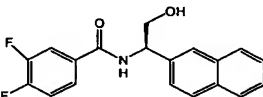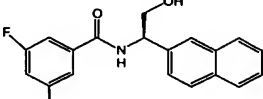
Examples 47 - 91 were prepared from the appropriate corresponding acid
20 using the same general procedure as described in Example 46.

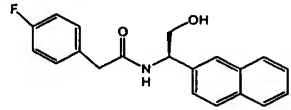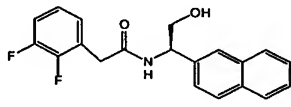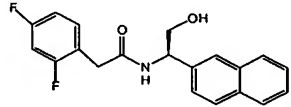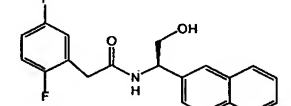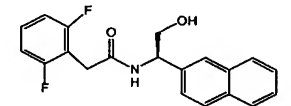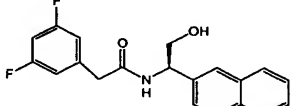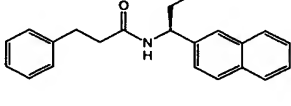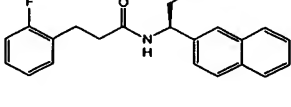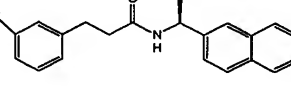| Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass (M+H)$^+$ m/z
47		(R)- 3-(3-Fluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide	1.40 (d)	336
48		(R)- 3-(4-Fluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide	1.40 (d)	336

Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass (M+H)$^+$ m/z
49		(R)- N-(1-Naphthalen-2-yl-ethyl)-3-phenyl-acrylamide	1.36 (d)	318
50		(R)- 3-(2-Chloro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide	1.46 (d)	356
51		(R)- 3-(3-Chloro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide	1.50 (d)	356
52		(R)- N-(2-Hydroxy-1-naphthalen-2-yl-ethyl)-3-o-tolyl-acrylamide	1.44 (d)	332
53		(R)- N-(2-Hydroxy-1-naphthalen-2-yl-ethyl)-3-m-tolyl-acrylamide	1.45 (d)	332
54		(R)- 3-(2,3-Difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide	1.45 (d)	354
55		(R)- 3-(2,4-Difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide	1.45 (d)	354
56		(R)- 3-(2,5-Difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide	1.44 (d)	354
57		(R)- 3-(2,6-Difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide	1.44 (d)	354

| Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass (M+H)$^+$ m/z
58		(R)- 3-(3,4-Difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide	1.45 (d)	354
59		(R)- 3-(3,5-Difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide	1.46 (d)	354
60		(R)- 3-(4-Chloro-2-fluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide	1.54 (d)	370
61		(R)- 3-(2-Chloro-4-fluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acrylamide	1.52 (d)	370
62		(R)-Cyclopentane-carboxylic acid (2-hydroxy-1-naphthalen-2-yl-ethyl)-amide	1.53 (f)	284
63		(R)-Cyclohexane-carboxylic acid (2-hydroxy-1-naphthalen-2-yl-ethyl)-amide	1.63 (f)	298
64		(R)-2-Cyclopentyl-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acetamide	1.65 (f)	298
65		(R)-2-Cyclohexyl-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acetamide	1.75 (f)	312
66		(R)-N-(2-Hydroxy-1-naphthalen-2-yl-ethyl)-benzamide	1.51 (f)	292

Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass (M+H)$^+$ m/z
67		(R)-2-Fluoro-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-benzamide	1.52 (f)	310
68		(R)-3-Fluoro-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-benzamide	1.59 (f)	310
69		(R)-4-Fluoro-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-benzamide	1.57 (f)	310
70		(R)-2,3-Difluoro-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-benzamide	1.57 (f)	328
71		(R)-2,4-Difluoro-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-benzamide	1.58 (f)	328
72		(R)-2,5-Difluoro-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-benzamide	1.56 (f)	328
73		(R)-2,6-Difluoro-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-benzamide	1.42 (f)	328
74		(R)-3,4-Difluoro-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-benzamide	1.65 (f)	328
75		(R)-3,5-Difluoro-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-benzamide	1.66 (f)	328
76		(R)-2-(2-Fluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acetamide	1.54 (f)	324
77		(R)-2-(3-Fluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acetamide	1.57 (f)	324

Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass $(M+H)^+$ m/z
78		(R)-2-(4-Fluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acetamide	1.58 (f)	324
79		(R)-2-(2,3-Difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acetamide	1.59 (f)	342
80		(R)-2-(2,4-Difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acetamide	1.60 (f)	342
81		(R)-2-(2,5-Difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acetamide	1.57 (f)	342
82		(R)-2-(2,6-Difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acetamide	1.54 (f)	342
83		(R)-2-(3,5-Difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-acetamide	1.64 (f)	342
84		(R)-N-(2-Hydroxy-1-naphthalen-2-yl-ethyl)-3-phenyl-propionamide	1.65 (f)	320
85		(R)-3-(2-Fluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-propionamide	1.67 (f)	338
86		(R)-3-(3-Fluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-propionamide	1.65 (f)	338

Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass (M+H)+ m/z
87		(R)-3-(4-Fluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-propionamide	1.67 (f)	338
88		(R)-3-(2,3-Difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-propionamide	1.69 (f)	356
89		(R)-3-(2,4-Difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-propionamide	1.69 (f)	356
90		(R)-3-(2,5-Difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-propionamide	1.67 (f)	356
91		(R)-3-(3,4-Difluoro-phenyl)-N-(2-hydroxy-1-naphthalen-2-yl-ethyl)-propionamide	1.68 (f)	356

EXAMPLE 92

(R) -3-(2,6-Difluoro-phenyl)-N-[2-hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-acrylamide
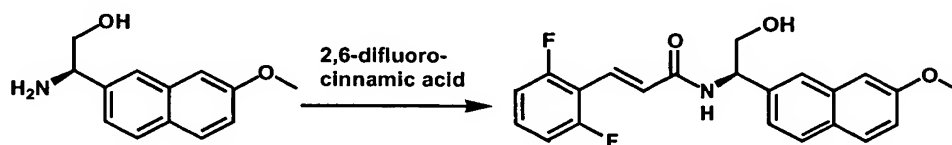
A mixture of (R)-2-Amino-2-(7-methoxy-naphthalen-2-yl)-ethanol (0.1 mmol), 2,6-difluorocinnamic acid (0.1 mmol), EDC•HCl (0.2 mmol), DMAP (0.1 mmol), triethyl amine (0.3 mmol) in dichloromethane (2 mL) was stirred at

room temperature for 14 h. The reaction mixture was purified by flash chromatography eluting with 5% methnol in ethyl acetate to provide the title compound as a solid (25 mg).

5 ^{1}H NMR (CDCl$_3$): δ 7.78-7.66 (m, 4 H), 7.30 (d, J = 8.4 Hz, 1 H), 7.15-7.02 (m, 5 H), 6.32 (d, J = 15.6 Hz, 1 H), 5.35-5.28 (m, 1 H), 4.07-4.01 (m, 2 H), 3.90 (s, H).

MS (M+H)$^+$ 384.

10 ## EXAMPLES 93 - 103

Examples 93 - 103 were prepared from the appropriate corresponding acid using the same general procedure as described in Example 92.

Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass (M+H)$^+$ m/z
93		(R)- 3-(2-Fluoro-phenyl)-N-[2-hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-acrylamide	1.54 (d)	366
94		(R)- 3-(3-Fluoro-phenyl)-N-[2-hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-acrylamide	1.55 (d)	366
95		(R)- 3-(4-Fluoro-phenyl)-N-[2-hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-acrylamide	1.55 (d)	366
96		(R)- N-[2-Hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-3-phenyl-acrylamide	1.52 (d)	348

Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass (M+H)⁺ m/z
97		(*R*)- 3-(2-Chloro-phenyl)-N-[2-hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-acrylamide	1.61 (d)	382
98		(*R*)- 3-(3-Chloro-phenyl)-N-[2-hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-acrylamide	1.65 (d)	382
99		(*R*)- N-[2-Hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-3-o-tolyl-acrylamide	1.59 (d)	362
100		(*R*)- 3-(2,3-Difluoro-phenyl)-N-[2-hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-acrylamide	1.66 (d)	384
101		(*R*)- 3-(2,4-Difluoro-phenyl)-N-[2-hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-acrylamide	1.64 (d)	384
102		(*R*)- 3-(2,5-Difluoro-phenyl)-N-[2-hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-acrylamide	1.64 (d)	384
103		(*R*)- 3-(2-Chloro-4-fluoro-phenyl)-N-[2-hydroxy-1-(7-methoxy-naphthalen-2-yl)-ethyl]-acrylamide	1.72 (d)	400

EXAMPLE 104

(1*R*, 2*S*)-3-*tert*-butoxycarbonylamino-2-hydroxy-3-naphthalen-2-yl-propionic
acid methyl ester

cinnamic acid

5
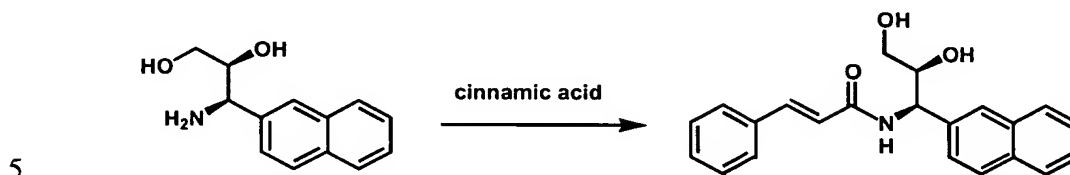
A solution of (3*R*,2*S*)-3-amino-3-naphthalen-2-yl-propane-1,2-diol (0.1
mmol), cinnamic acid (0.1 mmol), EDC•HCl (0.2 mmol), DMAP (0.1 mmol),
triethyl amine (0.3 mmol) in dichloromethane (2 mL) was stirred at room
10 temperature for 14 h. The reaction mixture was purified by flash chromatography
eluting with 5% methnol in ethyl acetate to provide the title compound as a solid
(20 mg).

HPLC rt: 1.49 (method d)
15 ^{1}H NMR (CD$_3$OD): δ 7.88-7.43 (m, 4 H), 7.68 (d, *J* = 15.5 Hz, 1 H), 7.49-7.43
(m, 5 H),7.35-7.26 (m, 3 H), 6.54 (brs, 1 H), 6.52 (d, *J* = 15.5 Hz, 1 H), 5.45 (dd,
J = 8, 4, Hz, 1 H), 4.21 (q, *J* = 5.5 Hz, 1 H), 3.61 (d, *J* = 6 Hz, 2 H).
MS (M+H)$^+$ 370.

20 ## EXAMPLES 105 - 115

Examples 105 - 115 were prepared from the appropriate corresponding
acid using the same general procedure as described in Example 104.

Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass (M+H)$^+$ m/z
105		(1*R,2S*)- N-(2,3-Dihydroxy-1-naphthalen-2-yl-propyl)-3-(2-fluoro-phenyl)-acrylamide	1.52 (d)	366

Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass (M+H)⁺ m/z
106		(1*R*,2*S*)- 3-(2-Chloro-phenyl)-N-(2,3-dihydroxy-1-naphthalen-2-yl-propyl)-acrylamide	1.60 (d)	382
107		(1*R*,2*S*)- 3-(3-Chloro-phenyl)-N-(2,3-dihydroxy-1-naphthalen-2-yl-propyl)-acrylamide	1.63 (d)	382
108		(1*R*,2*S*)- N-(2,3-Dihydroxy-1-naphthalen-2-yl-propyl)-3-o-tolyl-acrylamide	1.60 (d)	362
109		(1*R*,2*S*)- N-(2,3-Dihydroxy-1-naphthalen-2-yl-propyl)-3-p-tolyl-acrylamide	1.88 (d)	362
110		(1*R*,2*S*)- 3-(2,3-Difluoro-phenyl)-N-(2,3-dihydroxy-1-naphthalen-2-yl-propyl)-acrylamide	1.85 (d)	384
111		(1*R*,2*S*)- 3-(2,4-Difluoro-phenyl)-N-(2,3-dihydroxy-1-naphthalen-2-yl-propyl)-acrylamide	1.86 (d)	384
112		(1*R*,2*S*)- 3-(3,4-Difluoro-phenyl)-N-(2,3-dihydroxy-1-naphthalen-2-yl-propyl)-acrylamide	1.87 (d)	384
113		(1*R*,2*S*)- 3-(3,5-Difluoro-phenyl)-N-(2,3-dihydroxy-1-naphthalen-2-yl-propyl)-acrylamide	1.89 (d)	384

Example No.	Structure	Chemical Name	HPLC rt (min), method	Mass (M+H)$^+$ m/z
114		(1*R*,2*S*)- 3-(4-Chloro-2-fluoro-phenyl)-N-(2,3-dihydroxy-1-naphthalen-2-yl-propyl)-acrylamide	1.94 (d)	400
115		(1*R*,2*S*)- 3-(2-Chloro-4-fluoro-phenyl)-N-(2,3-dihydroxy-1-naphthalen-2-yl-propyl)-acrylamide	1.92 (d)	400

EXAMPLE 116

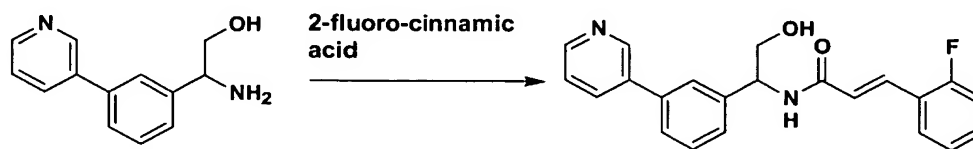### N-[2-Hydroxy-1-(3-pyridin-3-yl-phenyl)-ethyl]-3-phenyl-acrylamide

5
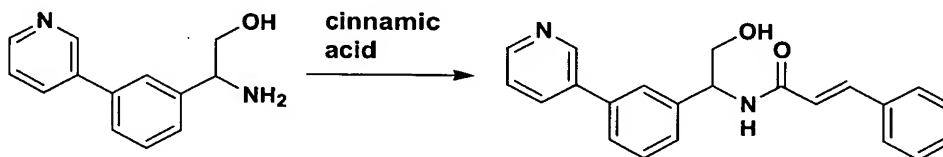
To a solution of cinnamic acid (0.083 mmol), amine (0.064 mmol), EDC (18.4 mg, 0.096 mmol), HOBT (13 mg, 0.096 mmol) in DMF (2 mL) was added

10   diisopropylethylamine (33 μL, 0.192 mmol), and the resulting reaction mixture was stirred at room temperature for 18. The residue was purified by preparative HPLC (Primeshere C18-HC 21.2x100 mm; (5mM NH₄OAc) 0-100% gradient over 5 min; 20 mL/min flow rate) to afford the title product.

15   HPLC rt: 1.49 min (method e)

^{1}H NMR (CDCl₃): δ 4.03 (d, 3 H, *J* = 4.6 Hz), 5.29 (m, 1 H), 6.51 (d, 1H, *J* = 15.7 Hz), 6.54 (s, 1H), 7.3-7.5 (m, 9H), 7.53 (s, 1H) 7.67 (d, 1H, *J* = 15.7 Hz), 7.84 (d, 1H, *J* = 7.8 Hz), 8.57 (dd, 1H, *J* = 1.8, 4.8 Hz), 8.71 (d, 1H, *J* = 1.8 Hz). Mass (M+H)$^+$ 345.

20

EXAMPLE 117

3-(2-Fluoro-phenyl)-N-[2-hydroxy-1-(3-pyridin-3-yl-phenyl)-ethyl]-acrylamide

5

To a solution of 2-fluoro-cinnamic acid (0.083 mmol), amine (0.064 mmol), EDC (18.4 mg, 0.096 mmol), HOBT (13 mg, 0.096 mmol) in DMF (2 mL) was added diisopropylethylamine (33 µL, 0.192 mmol), and the resulting reaction mixture was stirred at room temperature for 18. The residue was purified by preparative HPLC (Primeshere C18-HC 21.2x100 mm; (5mM NH$_4$OAc) 0-100% gradient over 5 min; 20 mL/min flow rate) to afford the title product.

HPLC rt: 1.51 min (method e)

Mass (M+H)$^+$ 363.